

Assessment of prognostic value of semiquantitative parameters on gated single photon emission computed tomography myocardial perfusion scintigraphy in a large middle eastern population

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ABSTRACT

Objectives: Coronary artery disease is the leading cause of mortality worldwide. The goal of this study is to determine the prognostic value of semiquantitative parameters of electrocardiogram-gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in a large Middle Eastern (Iranian) population. **Materials and Methods:** This study was a prospective study including all patients referred to our center for myocardial perfusion scan. The patients were followed annually up to 24 months and their survival information was collected. **Results:** From 1148 patients, 473 (41.2%) men and 675 (58.8%) women, 40.6% had normal MPI, 13.3% near normal and 46.1% abnormal MPI. After follow-up of 929 patients, 97.4% of patients were alive, and 2.6% succumbed to cardiac deaths. Abnormal ejection fraction was related with cardiac events ($P = 0.001$), but neither transient ischemic dilation (TID) ($P = 0.09$) nor lung/heart ratio ($P = 0.92$) showed such relationship. Association between summed difference score (SDS) and soft cardiac events ($P < 0.001$) was significant. Summed motion score (SMS) and summed thickening score (STS) showed a significant relation with hard cardiac events, including myocardial infarction and cardiac death ($P < 0.001$ and $P = 0.001$, respectively). Totally, risk of all cardiac events was significantly higher in abnormal MPI group than normal group ($P < 0.001$, 0.02, and 0.025, respectively). No significant relationship was found between TID and total cardiac events ($P = 0.478$). **Conclusion:** Semiquantitative variables derived from gated SPECT MPI have independent prognostic value. Rate of total cardiac events is higher in patients with higher summed stress score and SDS. Total and hard cardiac events are higher in upper scores of functional parameters (SMS and STS). Total cardiac events are higher in patients with lower left ventricular ejection fraction.

Keywords: Myocardial perfusion scintigraphy, prognosis, semiquantitative, single photon emission computed tomography

INTRODUCTION

Coronary artery disease (CAD) is still the most common cause of death worldwide.^[1-3] Beside diagnostic applications, the prognostic value of myocardial perfusion imaging (MPI) has been well established.^[4,5] Normal MPI by semiquantitative visual interpretation is associated with low risk of future cardiac

events (<1%) in different studies.^[4,6-14] Myocardial single photon emission computed tomography (SPECT) can identify low-risk patients in whom medical conservative therapy is sufficient, thus avoiding unnecessary aggressive interventions.^[7,11,15,16] Electrocardiographic (ECG)-gated SPECT, estimates the risk of future cardiac events by representing the extent of ischemia and global left ventricular (LV) function.^[5]

In this study, we evaluated the prognostic value of ECG-gated myocardial SPECT in a large number of middle Eastern (Iranian) patients with special focus on independent prognostic value of each semiquantitative parameters calculated by automated Auto Quant program software (Cedars-Sinai, Los Angeles, California, USA).

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MATERIALS AND METHODS

Patient selection

A total of 1148 consecutive patients referred for myocardial perfusion SPECT to research center for nuclear medicine, Shariati Tertiary Grand Hospital, Tehran, Iran, in a duration of 19 months (from May 2010 to November 2011) were enrolled in this study. All patients with suspected or known CAD were studied, and no exclusion criteria were used. Relevant information regarding patients' demographic data and risk factor assessment, were used to complete detailed questionnaires.

The study design was prospective, but as no intervention was made, ethical clearance was not obtained.

Stress type

Single photon emission computed tomography imaging was performed 15–30 min after treadmill exercise according to Bruce protocol. For nonasthmatic patients unable to exercise, dipyridamole (0.56 mg/kg) and for patients with asthma or chronic obstructive pulmonary disease, dobutamine infusion (5–10 µg/kg/min for 3 min, with the dose increase every 3 min until a maximum dose of 40 µg/kg/min) were used as pharmaceutical stress. Stress end points were determined according to AACC/AHA practice guidelines as below: Drop in systolic blood pressure of >10 mm Hg from baseline blood pressure despite an increase in workload (when accompanied by other evidence of ischemia), moderate to severe angina, increasing nervous system symptoms (e.g. ataxia, dizziness, or near-syncope), signs of poor perfusion (cyanosis or pallor), technical difficulties in monitoring ECG or systolic blood pressure, patient's desire to stop, sustained ventricular tachycardia and ST elevation (≥1.0 mm) in leads without diagnostic Q-waves (other than V1 or aVR).

Radiopharmaceutical

Myocardial perfusion imaging was performed with thallium-201 (Tl-201) in 20 (1.7%) and technetium methoxyisobutylisonitrile (Tc-MIBI) in 1128 (98.3%) patients.

When thallium was used (3–4 mCi), imaging was performed 10–15 min after exercise stress, 5–10 min after pharmacologic stress and 45 min after injection in the rest phase.

When MIBI (25–30 mCi in stress and 20 mCi in rest phase according to 2 days protocol) was used imaging was performed 15–30 min after exercise stress test, 45–60 min after pharmacologic stress and 45–60 min after injection in rest phase of the study.

Imaging

Electrocardiogram-gated myocardial perfusion SPECT was performed by a dual head ADAC/PHILIPS gamma camera (Circular 180°, 32 projections, 25 s/projection). Female patients were imaged in supine and male patients in the prone position. No attenuation correction was applied.

Image analysis and interpretation

Semiquantitative analysis was performed using Auto Quant program software from Cedars-Sinai, Los Angeles, California, USA (Quantitative Perfusion SPECT [QPS], Quantitative Gated SPECT [QGS]). Visual scan interpretation was performed by at least two experienced nuclear physicians according to four points, 20 segment scoring system. Each segment scores 0–4 (0: normal, 1: mild reduction of uptake, 2: moderate reduction of uptake, 3: severe reduction of uptake, 4: absence of uptake). Based on visual scan findings, patients are divided in three groups; “Normal” if total score is 0; “near normal” if total score is 1 and “abnormal” if total score is 2 and more.

Semiquantitative parameters are extracted from an automated program of Auto Quant (QPS, QGS) which is commercially available. The heart is divided into 20 segments, and each segment is again scored as: 0 = normal, 1 = mild reduction of uptake, 2 = moderate reduction of uptake, 3 = severe reduction of uptake, 4 = absence of uptake. Summed stress score (SSS) is obtained from the total amount of scores in all 20 segments in the stress images and represents total myocardial ischemia and infarct. Summed rest score (SRS) similarly shows the scores in the rest phase and represents infarcted myocardium. Summed difference score (SDS) shows the difference of myocardial scores in stress and rest phases, representing the amount of ischemic myocardium. Summed motion score (SMS) shows myocardial functional movements, and is obtained from total motion scores in all 20 myocardial segments: 0 normal, 1 mild hypokinesia, 2 moderate hypokinesia, 3 severe hypokinesia, 4 akinesia and 5 dyskinesia. Summed thickening score (STS) shows myocardial thickening, and is obtained from total thickening scores in 20 myocardial segments: 0 normal thickening, 1 mildly decreased thickening, 2 moderately decreased thickening, 3 severely decreased thickening and 4 absent thickening.

According to these semiquantitative parameters, patients are grouped in 4 categories; scores 1–3 (<4) in the first category, 4–8 in the second, 9–13 in the third and >13 in the fourth category.

Transient ischemic dilation (TID) shows abnormal dilatation of the left ventricle in the stress phase. The automated software represents TID as a ratio of LV volume at stress and rest images after calculation of endocardial LV volumes. TID more than 1.20 was considered abnormal.

Left ventricular ejection fraction (LVEF) is also calculated by estimation of end diastolic and end systolic volumes (EDV and ESV) derived from short axis images. LVEF <50% was considered abnormal.

Follow-up

Patients were followed annually up to 24 months after MPI. Patients were followed-up by phone interview. Cardiac death and myocardial infarction (MI) were defined as hard while coronary artery bypass graft (CABG) surgery or coronary angioplasty as soft cardiac events. 26 (2.3%) and 11 (1%) patients had undergone

percutaneous transluminal coronary angioplasty and CABG respectively. Other patients received medical therapy on the basis of MPI results. Event-free survival was calculated from the time of MPI to soft/hard events.

Statistical analysis

We used SPSS statistical software (SPSS version 17.0, SPSS Inc., Chicago) for statistical analysis. For survival assessments we used Kaplan–Meier and Cox-Regression tests. To evaluate the relations between semiquantitative variables and cardiac events univariate analysis was used. A multivariate logistic regression was also applied with consideration of all semi-quantitative parameters. $P < 0.05$ was considered as statistically significant.

RESULTS

1148 patients, 473 (41.2%) men and 675 (58.8%) women were studied. Age range was between 17 and 90 years with a mean of 57.99 ± 11.6 .

After visual image interpretation, 466 patients (40.6%) had normal, 303 patients (26.4%) near normal and 379 patient (33%) abnormal MPI. Among basic risk factors, only smoking was found to be in correlation with MPI results ($P < 0.001$) [Table 1].

In the survival analysis, 929 patients were included. From total 1148 patients, 204 patients were lost to follow-up, and 15 patients expired due to noncardiac reasons, and were excluded from the study. After mean follow-up duration of 18 ± 3 (median: 19 months), 95.9% (905 patients) were alive and 2.5% (24 patients) had cardiac deaths.

Patients with normal MPI results had significantly longer survival rates than those with abnormal scans (21.45 vs. 19.84 months, $P < 0.001$) [Figure 1].

The study demonstrated the basic risk factors were not significantly related with cardiac events [Table 2], while the MPI result was significantly associated with these factors (odds ratio [OR]: 2.32, confidence interval [CI] = 1.391–5.716, $P = 0.004$).

Risk of total, soft and hard cardiac events were significantly higher in abnormal MPI group than those with normal scintigraphy according to the visual analysis [Table 3].

Table 1: Cardiovascular risk factors according to scan perfusion results

Risk factor	Scan result (%)		OR CI 95%*	P
	Normal or near normal	Abnormal		
Hypertension	336 (43.8)	151 (39.9)	0.66-1.09	0.228
Diabetes mellitus	201 (26.2)	114 (30.2)	0.92-1.59	0.16
Hyperlipidemia	289 (37.6)	135 (35.7)	0.71-1.19	0.558
Smoking	107 (14)	87 (35.7)	1.34-2.52	<0.001
Family history of CAD	103 (13.4)	62 (16.5)	0.90-1.79	0.179

CAD: Coronary artery disease, OR: Odds ratio, CI: Confidence interval, * $P < 0.05$

Overall, among semiquantitative MPI parameters, all (SSS, SDS, SMS, STS, EDV, ESV) but SRS are shown to be associated with cardiac events [Table 4].

Total cardiac events are more frequent in all higher SSS, SDS, SMS and STS categories. Relationship between SDS and soft cardiac event ($P < 0.001$), SMS and STS with hard cardiac events is especially significant ($P < 0.001$, and $P = 0.001$, respectively). However, no relation was found between cardiac events and higher SRS and TID categories [Table 3].

By applying all semiquantitative parameters in a multivariate logistic regression analysis, SDS category >3 was detected as the only significant predictor of cardiac events (OR = 5.3; CI 95% = 1.27–22.57; $P = 0.023$) [Table 4].

Among other indices including ejection fraction (EF), TID and lung/heart ratio, only EF demonstrated strong relationship ($P = 0.001$) with cardiac events [Table 5].

DISCUSSION

Myocardial perfusion imaging with radionuclide was first introduced in 1970s and soon it was used routinely as a diagnostic tool in CAD.^[17] Besides diagnostic role, MPI shows incremental value in the determination of prognosis, risk stratification and treatment strategies of these patients.^[7,18] The present study which is a prospective study on a large number of middle eastern (Iranian) population, confirms the prognostic value of ECG-gated MPI.

Survival rate in normal MPI is significantly higher than abnormal MPI group. Risks of total, hard and soft events are also higher in abnormal MPI patients. Different studies have shown similar results. In normal MPI group, risk of hard cardiac events (cardiac death or nonfatal MI) are $<1\%$ in 1-year, independent from type of radiotracer (Tc-99 m sestamibi or Tl-201 chloride), stress type (exercise or pharmacologic) or history of CAD.^[4,6-9,12-14,16] In patients with abnormal MPI studies, however, this risk increases.^[10-12] Shaw *et al.* showed overall CAD event rates were

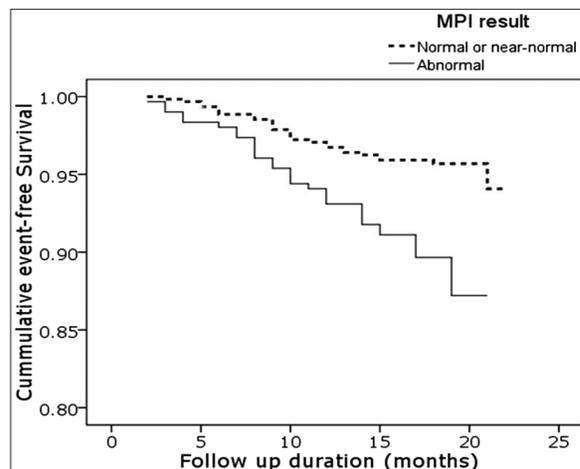


Figure 1: Event-free survival according to myocardial perfusion imaging result

1.2%, 8%, and 10% for patients with 0%, 1–4.9%, and $\geq 5\%$ ischemic myocardium, respectively.^[10]

More significantly, our study shows similar results on the basis of semiquantitative data represented by Auto Quant application (QPS/QGS, from Cedars-Sinai). Rate of total cardiac events are significantly higher in patients with higher amount of ischemic scores according to SSS (SSS, 4.6% in category 1 vs. 11.7% in category 4) and SDS (SDS, 4.4% in category 1 vs. 14% in category 4) calculated by automated QPS. These scores represent ischemic myocardium at risk. As expected, no such relation is found with SRS which represents myocardial perfusion defects in the rest phase (myocardial scar).

Nishimura *et al.* have shown similar results. During a follow-up duration of 3 years, rate of major cardiac events has been 2.31% and 9.21% in normal and severely abnormal SSS, respectively.^[19]

Our study shows that the quantitative assessment of myocardial function derived from parameters of QGS has independent prognostic value. Total and hard cardiac events, as opposed to soft events are significantly more in patients with higher summed motion and STSs (total cardiac events: 3.4% in SMS category 1 and 3% in STS category 1, in comparison to 11.7% and 11% respectively in category 4). Similar results have been shown in relation to hard cardiac events. Therefore, SMS and STS can be considered independently as prognostic factors in risk stratification of patients with suspected CAD.

J-ACCESS study has shown the prognostic significance of data derived from QGS. This study showed that major cardiac events are higher in patients with lower EF ($<45\%$) and higher ESV.^[19] Our study also shows the prognostic value of post-stress LVEF. EF is significantly lower in patients with cardiac events (51.5% vs. 60%). Sharir *et al.* also showed the prognostic importance of LVEF in ECG Gated SPECT, as in patients with EF $<45\%$ and ESV <70 , risk of cardiac death was 7.9%/year.^[20]

A sub-analysis of J-ACCESS study also revealed that moderate to high amounts of SSS and higher ESV index derived from stress gated perfusion SPECT are independent values in prediction of refractory heart failure in patients with known or suspected CAD.^[21]

Fukuda have shown a higher risk of cardiac events in patients with transient LV dilation on thallium-201 stress MPI. The event rate is particularly high for exercise stress MPI.^[22]

Table 2: Odds of cardiac events based upon the risk factors of CAD

Risk factors	P	OR	95% CI for OR*	
			Lower	Upper
Hypertension	0.487	0.776	0.379	1.587
Diabetes mellitus	0.717	1.147	0.546	2.407
Smoking	0.904	0.942	0.358	2.479
Family history	0.127	1.85	0.840	4.075
Sex	0.638	0.834	0.392	1.776

CAD: Coronary artery disease, OR: Odds ratio, CI: Confidence interval, *P: <0.05

Table 3: Cardiac event rate according to qualitative and semiquantitative scan perfusion SPECT

Variable	Grouping	Total cardiac event			Hard cardiac event			Soft cardiac event		
		Number	Percentage	P*	Number	Percentage	P*	Number	Percentage	P*
MPI result	Normal (n=619)	28	4.50	0.000	13	2.1	0.025	15	2.4	0.002
	Abnormal (n=308)	35	11.3		15	4.9		21	6.8	
SSS category	1 (n=633)	29	4.6	0.026	14	2.2	0.17	10	1.5	0.032
	2 (n=112)	9	8		2	1.7		8	7.1	
	3 (n=38)	2	5.2		1	2.6		1	2.6	
	4 (n=102)	12	11.7		6	5.8		6	5.8	
SDS category	1 (n=698)	31	4.4	0.002	16	2.2	0.114	16	2.2	0.000
	2 (n=129)	16	12.4		5	3.8		12	9.3	
	3 (n=34)	2	5.8		0	0		2	5.8	
SRS category	4 (n=21)	3	14		2	9		1	4	
	1 (n=770)	41	5.3	0.336	17	2.2	0.85	25	3.2	0.52
	2 (n=35)	3	8.5		2	5.7		1	2.8	
	3 (n=22)	2	9		0	0		2	9	
TID category	4 (n=58)	6	10.3		4	6.8		2	3.4	
	<1.19 (n=791)	45	5.6	0.478	19	2.4	0.28	26	3.2	0.52
	≥ 1.20 (n=91)	7	7.7		4	4.3		4	4.3	
SMS category	1 (n=379)	13	3.4	0.001	3	0.7	0.000	10	2.6	0.24
	2 (n=181)	11	6		6	3.3		5	2.30	
	3 (n=97)	3	3		0	0		3	2.7	
	4 (n=211)	24	11.3		13	6.1		12	5.6	
STS category	1 (n=556)	21	3.7	0.004	8	1.4	0.001	13	2.3	0.086
	2 (n=114)	9	7.8		2	1.7		7	6.1	
	3 (n=64)	6	9.3		2	3		4	6.2	
	4 (n=136)	15	11		10	7.3		6	4.4	

MPI: Myocardial perfusion imaging, SSS: Summed stress score, SDS: Summed difference score, SRS: Summed rest score, SMS: Summed motion score, STS: Summed thickening score, TID: Transient ischemic dilation; SPECT: Single photon emission computed tomography, *P: <0.05

Table 4: Semiquantitative SPECT parameters in patients with and without cardiac events

Semiquantitative SPECT parameters	Cardiac event		P#
	Yes	No	
SSS	520.13 (1.50)*	433.35 (1.00)	0.011
SRS	470.52 (0.00)	436.48 (0.00)	0.199 NS
SDS	530.20 (1.50)	431.10 (1.00)	0.003
SMS	546.70 (10.00)	422.63 (5.00)	<0.0001
STS	550.95 (5.00)	422.37 (1.00)	<0.0001
EDV	534.68 (69.50)	424.34 (57.00)	0.002
ESV	559.48 (28.50)	422.74 (21.00)	<0.0001

*Mean rank (median), *Significant with Man-Witney U-test. NS: Not significant, SSS: Summed stress score, SDS: Summed difference score, SRS: Summed rest score, SMS: Summed motion score, STS: Summed thickening score, SPECT: Single photon emission computed tomography, EDV: End diastolic volume, ESV: End systolic volume, *P: <0.05

Table 5: Other semiquantitative SPECT parameters in patients with and without cardiac events

Semiquantitative parameters in QGS	Cardiac event		P
	Yes	No	
EF	51.52±18.147	60.42±14.429	<0.0001
TID	1.0504±0.13441	1.0136±0.15391	0.09
LHR	0.3382±0.06751	0.3369±0.09717	0.928

QGS: Quantitative gated SPECT, SPECT: Single photon emission computed tomography, TID: Transient ischemic dilation, EF: Ejection fraction, LHR: Lung/heart ratio

Even in patients with otherwise normal MPI, TID shows incremental prognostic value. Total cardiac events are higher in patients with TID, regardless of stress type.^[23] However, in our study the relation between TID and cardiac events was not statistically significant ($P = 0.09$).

LIMITATIONS

The quantitative data in some patients were not considered in analyses due to some technical problems such as patient's dysrhythmia, high-level visceral uptake, ... leading to infeasibility or unreliability of semiquantitative analysis.

Some patients were failed follow-up due to unavailable or changed phone numbers, traveling, etc. Better system and information registry are needed in the future to provide more reliable and available data.

CONCLUSION

Semiquantitative values obtained by gated SPECT myocardial perfusion scintigraphy have a great value in determining prognosis in patients with known or suspected CAD. In general, patients with abnormal scintigraphy have a higher risk of cardiac events. Lower EF rate and higher SSS, SDS, SMS and STS are significantly related to higher incidence of total cardiac events; however SDS is mainly related to soft cardiac events, and SMS and STS to hard cardiac events.

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